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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/479,038	06/07/95	DROHAN	W 1327.0440006

18M1/1030

STERNE KESSLER GOLDSTEIN AND FOX
1100 NEW YORK AVENUE N W
SUITE 600
WASHINGTON DC 20005-3934

EXAMINER	
ZEMAN, M	

ART UNIT	PAPER NUMBER
1815	16

DATE MAILED: 10/30/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

Responsive to communication(s) filed on 7/7/97.

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- Claim(s) 1-33 is/are pending in the application.
- Of the above, claim(s) 1-11 + 21-23 is/are withdrawn from consideration.
- Claim(s) _____ is/are allowed.
- Claim(s) 12-20 + 24-33 is/are rejected.
- Claim(s) _____ is/are objected to.
- Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- Notice of Reference Cited, PTO-892
- Information Disclosure Statement(s), PTO-1449, Paper No(s). 13+15
- Interview Summary, PTO-413
- Notice of Draftsperson's Patent Drawing Review, PTO-948
- Notice of Informal Patent Application, PTO-152

DETAILED ACTION

1. Claims 12-33 are pending in this application. Claims 1-11 were withdrawn from consideration by the examiner as being drawn to a non-elected invention.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Applicant's arguments filed 7/7/97 have been fully considered but they are not persuasive.

4. Claims 12-20 and 27 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the previous office action.

Claims 12-20 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for fibrin matrices comprising antimicrobials, growth hormones and other proteins, does not reasonably provide enablement for fibrin matrices comprising antibodies, or methods of their use. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The invention claimed in pending claims 12-20 is a delivery system for the delivery of antibodies to a patient in a fibrin sealant matrix. The specification filed 6/7/95 details how to include antibiotics, chemotherapeutics and growth factors in the fibrin sealant, however there is no discussion of the inclusion of antibodies. In view of this, this application is accorded the filing date of the instant application, 6/7/95. Priority to earlier parent applications is denied for claims including antibodies as member of the fibrin matrix.

In the field of therapeutic antibodies, certain problems must be addressed. First, for the particular condition, wound, disease or cancer, appropriate antibodies must be selected that are problem-specific. These antibodies need to exhibit activity against their target in *in vitro* studies. Whether the antibody is still active after incorporation into the matrix must be assessed. Also, the ability of the antibody to be released from the matrix must also be studied. Once the compound has been delivered, the ability of the antibody to reach and react with its target must be determined. If the antibody is delivered in an implant, the release kinetics and resulting activity of the antibody are crucial pieces of information. If the implant is a fibrin matrix clot, the biochemistry of the inclusion of an antibody, its release from the fibrin matrix and its activity upon release need to be addressed.

There is no exact teaching in the art of the inclusion of specific antibodies into a fibrin matrix for use as a treatment, or passive immunization. When the teachings in the prior art are inadequate, the level of disclosure in a specification must be greater. The specification as filed does not address the problems listed above. No particular antibodies are discussed, nor are there demonstration of specific antibody activity. No binding kinetics or appropriate administration routes are disclosed. No antibody-release and activity information is discussed, nor are the biochemical and kinetic consequences of containment of an antibody within a fibrin clot identified. The pending claims require "sustained release" of the antibody, yet there is no demonstration that antibodies are released from the matrix, the kinetics of any release, nor any timetable of half-lives of antibiotics in this type of matrix. Also required are solid forms of the antibody, but there is no

discussion of preferred solidification methods. No explanation of an emulsified antibody is given. An emulsion of a large protein could behave in a different manner than antibodies solubilized in water.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. Claims 12-15, 17-20 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Cadoni.

Claim 12 is now amended to recite a host of supplements for the fibrin matix, including antimicrobials or antibiotics. Claims 13-15 and 17-20 further define that composition as being capable of sustained localized release in or near the target tissue of the patient, in various form.

Cadoni et al. (Cadoni et al 1990 Endoscopy 22 p 194-195) discloses the use of fibrin sealants comprising an antimicrobial for the treatment of fistula within the duodenum. The antibiotic is released locally over several days.

7. Claims 12-15, 17-20, and 29-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Sakurai.

Claims 29-33 specify that the supplement is an antimicrobial, that the composition comprises thrombin, factor XIII, and calcium, and is administered by a carrier in a solid form.

Sakurai et al (Sakurai et al 1992 J Controlled Release 18 p 39-44) disclose an implantable composition comprising fibrin, an antimicrobial, thrombin, factor XIII, calcium and other ingredients formed as a disk covered by Dacron. This composition allowed sustained local release of the antimicrobial.

8. Claims 12-20, and 29-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Greco et al..

Greco et al. 1991 J biomedical Materials Research vol 25 p 39-51) disclose compositions comprising fibrin matrices and a variety of antimicrobials including: Carbenicillin, Gentamycin, Clindamycin, Ampicillin, Tobramycin, Ceftazydime, Cefotaxim and Mezlocillin. These compositions also comprised thrombin, factor XIII, and calcium. These matrices could be implanted and offered local sustained release of those antibiotics.

9. Claims 12-15, 17-20, 24, and 29-33 are rejected under 35 U.S.C. 102(b) as being anticipated by JP 60-204725.

Claim 24 includes cytotoxins or cell proliferation inhibitors to the fibrin matrix.

JP 60-204725 discloses fibrin sealant compositions comprising antibiotics, cellular proliferation inhibitors, and plasmin inhibitors, as well as factor XIII and calcium. These compositions can offer sustained localized release of the antibiotics and agents.

10. Claims 12-15, 17-20, and 29-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Khadem.

Khadem (US Patent 5,552,452) discloses fibrin biomatrix compositions that comprise antibiotics, factor XIII, thrombin, calcium etc. Such compositions can offer sustained localized release of the antibiotics.

11. Claims 12-20 and 30-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Lontz.

Lontz discloses fibrin matrices comprising polysaccharides and glycoproteins. Antibiotics and other biomedical entities can be included. These compositions can offer localized sustained release of the included compounds.

12. Claims 12-20 and 29-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Stroetmann.

Stroetmann (US Patent 4,427,651) discloses fibrin compositions that upon mixing provide a fibrin matrix. These compositions comprise fibrin, thrombin, and thrombolytic inhibitor, and antibiotics as well as calcium. These compositions can provide localized sustained treatment and release of the included compounds.

13. Claims 12-20, 24 and 30-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Luck.

Luck (US Patent 4,619,913) discloses fibrin matrix compositions comprising cytotoxins and chemotherapeutic agents which are to be implanted in a patient. These compositions provide locaized sustained release of the cytotoxins.

14. Claims 12-20, and 29-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Wahlig.

Wahlig (US Patent 4,853,225) discloses fibrin matrix compositions comprising a variety of antibiotics to be implanted into a patient for localized controlled release of the antibiotic.

15. Claims 12-20, 25 and 30-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Juergensen.

Juergensen (US Patent 5,549,904) discloses fibrin matrices that comprise transglutaminase and transforming growth factor beta, transforming growth factor alpha, insulin-like grwoth factor, epidermal growth factor, platelet derived growth factor, tumor necrosis factor, fibroblast growth factor, and interleukins (cytokines). Calcium is also included. These compositions are used to treat bone disorders, ligament disorders, muscle disorders and many others. These compositions can be implanted, and provide localized sustained release of the included factors.

16. Claims 12-20 and 24-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Marx.

Marx (US Patent 5,607,694) discloses fibrin matrix compisitions comprising lipids and liposomes in addition to the basic components of thrombin, factor XIII and calcium. These lipids serve to release bioactive substances over a sustained period of time at the location of the matrix. Marx discloses the addition of immunoglobulins, protease inhibitors, drugs, vitamins, growth factors, hormones, steroids, antibiotics, tumoricidal and tumoristatic compounds, minerals, polysaccharides, anaesthetics, nucleic acids, and polynucleotides.

17. Claims 12-20, 27 and 30-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Gristina.

Gristina discloses compositions of fibrin and antibodies in a matrix that can be applied or implanted at wound sites. These compositions are effective at preventing infection.

18. Claims 12-20, 27 and 30-33 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 92/17206.

WO 92/17206 discloses wound healing compositions of fibrin matrices comprising antibodies. These compositions specifically, locally and sustainedly release the antibodies to the wound site.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Juergenson as applied to claims 12-20, 25 and 30-33 above, further in view of Gerhart.

As discussed above, Juergensen (US Patent 5,549,904) discloses fibrin matrix compositions comprising growth factors and other factors for the treatment of bone and cartilage disorders. Gerhart (US Patent 5,364,839) discloses the use of protease inhibitors and bone inductive proteins (BMP's 1-7) as well as growth factors in a biodegradable matrix for the treatment of bone and cartilage disorders. Gerhart does not specifically disclose the use of fibrin matrices, but does specify the usefulness of biodegradable matrices in the practice of the invention. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have included the bone incudctive proteins of Gerhart in the implantable fibrin matrices of Juergensen, as these proteins were shown to be effective in biodegradable matrices for the treatment of bone and cartilage disorders by Gerhart, and the treatment of such disorders is specifically disclosed by the protocols of Juergensen. The inclusion of the bone inductive proteins would have speeded the regeneration of bone in areas in which the matrix had been implanted.

21. Claims 12-20, 26 and 30-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Juergensen as applied to claims 12-20 25 and 30-33 above, further in view of Oppermann.

As discussed above, Juergensen (US Patent 5,549,904) discloses fibrin matrix compositions comprising growth factors and other factors for the treatment of bone and cartilage

disorders. Oppermann (US Patent 5,354,557) discloses osteogenic implants that comprise demineralized bone, bone inducing proteins, and minerals. These implants are supported by a collagen matrix. Oppermann does not specifically disclose the use of fibrin matrices, but does specify the usefulness of biodegradable matrices in the practice of the invention. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have included the bone incudctive proteins, minerals, and demineralized bone complexes of Oppermann in the implantable fibrin matrices of Juergensen, as these compositions were shown to be effective in biodegradable matrices for the treatment of bone and cartilage disorders by Oppermann, and the treatment of such disorders is specifically disclosed by the protocols of Juergensen. The inclusion of these compositions would have speeded the regeneration of bone in areas in which the matrix had been implanted.

22. Claims 12-20, 28 and 30-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weiner.

Weiner (US Patent 5,366,958) discloses lipid vesicles that can include oligonucleotides or polynucleotides, that comprise fibrinogen as well. These lipid/fibrinogen vesicles are disclosed by Weiner as having affinity for fibrin matrices. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the lipid/fibrinogen vesicles of Weiner having affinity for fibrin matrices in fibrin matrix implants, as these vesicles would be retained in the fibrin matrix, and allow for localized sustained release of the oligonucleotides enclosed within.

Conclusion

23. No claim is allowed.

24. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

25. This application is subject to the provisions of Public Law 103-465, effective June 8, 1995. Accordingly, since this application has been pending for at least two years as of June 8, 1995, taking into account any reference to an earlier filed application under 35 U.S.C. 120, 121 or 365(c), applicant, under 37 CFR 1.129(a), is entitled to have a first submission entered and considered on the merits if, prior to abandonment, the submission and the fee set forth in 37 CFR 1.17(r) are filed prior to the filing of an appeal brief under 37 CFR 1.192. Upon the timely filing of a first submission and the appropriate fee of $375 for a small entity under 37 CFR 1.17(r), the finality of the previous Office action will be withdrawn. If a notice of appeal and the appeal fee set forth in 37 CFR 1.17(e) were filed prior to or with the payment of the fee set forth in 37 CFR 1.17(r), the payment of the fee set forth in 37 CFR 1.17(r) by applicant will be construed as a request to dismiss the appeal and to continue prosecution under 37 CFR 1.129(a). In view of 35 U.S.C. 132, no amendment considered as a result of payment of the fee set forth in 37 CFR 1.17(r) may introduce new matter into the disclosure of the application.

If applicant has filed multiple proposed amendments which, when entered, would conflict with one another, specific instructions for entry or non-entry of each such amendment should be provided upon payment of any fee under 37 CFR 1.17(r).

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (703) 305-7133. The examiner can be reached between the hours of 8:00 am and 5:30 pm Monday through Thursday, and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marian Knode, can be reached on (703) 308-4311.

The fax number for this Art Unit is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

mkz
October 22, 1997

Marian C. Knode

MARIAN C. KNODE
SUPERVISORY PATENT EXAMINER
GROUP 1800